Letter to the Editor

Markers of liver injury and clinical outcomes in COVID-19 patients: A systematic review and meta-analysis

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To the Editor

Since January 2020 when it was first isolated in China, coronavirus disease 2019 (COVID-19) has spread throughout the world and caused substantial morbidity and mortality.(1) Despite the rapidly growing knowledge base on the clinical course of the disease, no therapeutic agents have been proven to be effective for COVID-19. Further clarification of the clinical course of the disease could help in the development of effective treatment strategies. Wang and colleagues in their recent elegant study to investigate characteristics and prognostic factors in 339 elderly patients with COVID-19, observed a high proportion of severe and critical cases as well as high fatality rates.(2) Common complications included bacterial infection, acute respiratory distress syndrome as well as liver enzyme abnormalities. In their analyses to explore prognostic factors for fatal outcomes, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were not found to be independently associated with the risk of mortality. Though it has been reported liver injury is more prevalent in severe cases of COVID-19,(3, 4) whether circulating levels of markers of liver injury could predict clinical outcomes in COVID-19 patients is uncertain. In this context, we aimed to determine the nature of the relationships of admission levels of five main markers of liver injury (ALT, AST, gamma-glutamyltransferase (GGT), alkaline phosphatase (ALP) and total bilirubin) with the risk of clinical outcomes in patients with COVID-19 using a systematic meta-analysis.

We conducted this review using PRISMA and MOOSE guidelines (**Supplementary Materials 1-2**) and in accordance with a registered protocol in the PROSPERO International prospective register of systematic reviews (CRD42020183672). MEDLINE, Embase, and The Cochrane library were searched from 2019 to 17 May 2020 for published studies reporting on relationships between admission levels of markers of liver injury (GGT, ALT, AST, ALP and total bilirubin) and clinical outcomes in patients with COVID-19. The detailed search strategy has been reported in **Supplementary Material 3**. Outcomes were categorised into severe illness and mortality. Mean differences (95% CIs) for comparing mean levels of circulating markers across outcomes and relative risks (RRs) (95% confidence intervals, CIs) for

associations between markers and outcomes were used as summary measures across studies.(5) The inverse variance-weighted method was used to effect estimates using random-effects models to minimize the effect of heterogeneity. STATA release MP 16 (StataCorp LP, College Station, TX, USA) was used for all statistical analyses.

Sixteen retrospective cohort studies comprising 10,540 COVID-19 patients were eligible (**Table 1; Supplementary Materials 4-5**). All studies were based in China. The average age at baseline ranged from approximately 38 to 71 years. Comparing elevated vs low levels of ALT and AST respectively, the RRs (95% CIs) of severe illness were 1.03 (0.23-2.15) and 2.09 (0.44-9.9) respectively. Pooled analysis of 9 studies each showed significantly higher levels of ALT and AST in COVID-19 patients with severe illness compared to patients without severe illness: mean differences (95% CIs) of 9.15 U/L (1.47, 16.82; p=0.02) and 12.60 U/L (8.43, 16.77; p<0.001) respectively (**Fig. 1A**)

In pooled results of two studies each, the RRs (95% CIs) of mortality associated with elevated ALT and AST were 3.35 (2.37-4.75) and 10.42 (7.05-15.40) respectively. In results from single studies, increased levels of ALP and total bilirubin were each associated with an increased risk of mortality (**Supplementary Material 6**). Admission levels of AST and total bilirubin were higher in those who died; whereas ALT levels were not significantly different in both groups: mean differences (95% CIs) of 17.13 U/L (11.25, 23.01; p<0.001); 4.21 µmol/l (3.97, 4.46; p<0.001) and 5.82 U/L (-2.57, 14.21; p=0.17) respectively. In single reports, levels of ALP and GGT were higher in those who died compared with survivors (**Fig. 1B**).

Taking the overall evidence together, the data supports a higher prevalence of elevated admission levels of markers of liver injury in severe or mortality due to COVID-19 disease, which suggests that patients with elevated levels of liver markers at baseline (during admission) had higher risks of developing worse outcomes in COVID-19. The likely explanation for the worse outcomes observed in patients with baseline elevated markers of liver injury (as seen in chronic liver disease) could be attributed to compromised immune status.(3, 4)

Irrespective of the fact that about 2-11% of patients with COVID-19 have liver comorbidities,(3) COVID-19 also causes liver injury. However, there is controversy regarding the causes of liver injury in COVID-19.(3, 4) Proposed explanations include (i) drug-induced liver injury; (ii) direct injury to the liver due to COVID-19 hepatitis(4); (iii) COVID-19 induced myositis(4); (iv) binding of SARS CoV-2 directly to angiotensin-converting enzyme 2 (ACE2) positive rich cholangiocytes and causing liver damage;(6) (v) hepatic congestion due to high levels of positive end expiratory pressure during mechanical ventilation;(4) and (vi) aggravation of liver injury by SARS CoV-2 in patients with pre-existing viral hepatitis.(7, 8) In the absence robust association studies and formal risk prediction analyses, the overall evidence suggests that increased baseline levels of markers of liver injury could predict poor outcomes. The global prevalence of chronic liver disease remains high and continues to increase. Treatment options for COVID-19 are currently supportive; hence, there should be more intensive monitoring of levels of markers of liver injury during admission so that therapeutic approaches can be individually tailored.

There are several limitations which deserve mention. First, the heterogeneous reporting of severe illness outcomes prompted the use of composite measures. Second, the possibility of patient overlap as all 16 studies were reported from China; there have been concerns with duplicate reporting of study participants in articles.(9) Third, due to the limited sample sizes and low events, some studies were unable to assess risk ratios to quantify the relationships. Finally, though we extracted data on baseline (admission) levels of these markers, studies were not very specific regarding the exact time of blood sampling in relation to the disease status; hence, these results may have some biases.

In conclusion, elevated admission levels of markers of liver injury particularly the aminotransferases, may be associated with progression to severe disease or death in COVID-19. Monitoring levels of these markers could assist in the optimum management of patients.

Conflict of interest

None.

Acknowledgements

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References

1. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020 Mar 28;395(10229):1054-62. PubMed PMID: 32171076. Epub 2020/03/15.

2. Wang L, He W, Yu X, Hu D, Bao M, Liu H, et al. Coronavirus disease 2019 in elderly patients: Characteristics and prognostic factors based on 4-week follow-up. J Infect. 2020 Mar 30. PubMed PMID: 32240670. Pubmed Central PMCID: PMC7118526. Epub 2020/04/03.

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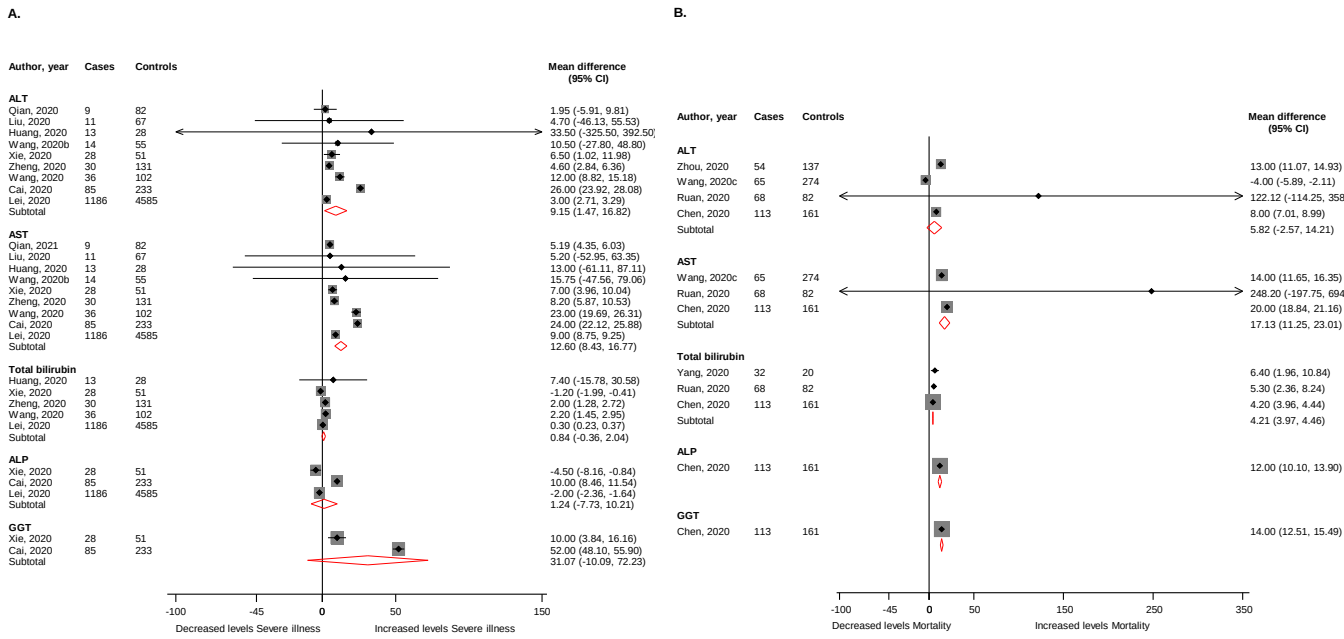
Fig. 1 Admission levels of markers of liver injury in (A) patients with or without severe COVID-19 illness and in (B) patients who died or survived



ALT, alanine aminotransferase; ALP, alkaline phosphatase; AST, aspartate aminotransferase; CI, confidence interval (bars); GGT, gamma-glutamyltransferase

SUPPLEMENTARY MATERIAL

Supplementary Material 1	PRISMA checklist
Supplementary Material 2	MOOSE checklist
Supplementary Material 3	MEDLINE literature search strategy
Supplementary Material 4	Selection of studies included in the meta-analysis
Supplementary Material 5	Reference list of included studies
Supplementary Material 6	Associations of markers of liver injury with risk of mortality in COVID-19 patients

Supplementary Material 1: PRISMA checklist

Section/topic	Item No	Checklist item	Reported on page No
Title			
Title	1	Identify the report as a systematic review, meta-analysis, or both	1
Abstract			
Structured summary	2	Provide a structured summary including, as applicable, background, objectives, data sources, study eligibility criteria, participants, interventions, study appraisal and synthesis methods, results, limitations, conclusions and implications of key findings, systematic review registration number	2
Introduction			
Rationale	3	Describe the rationale for the review in the context of what is already known	Introduction
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS)	Introduction
Methods			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (such as web address), and, if available, provide registration information including registration number	Methods
Eligibility criteria	6	Specify study characteristics (such as PICOS, length of follow-up) and report characteristics (such as years considered, language, publication status) used as criteria for eligibility, giving rationale	Methods
Information sources	7	Describe all information sources (such as databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched	Methods
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated	Supplementary Material 3
Study selection	9	State the process for selecting studies (that is, screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis)	Methods
Data collection process	10	Describe method of data extraction from reports (such as piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators	Methods
Data items	11	List and define all variables for which data were sought (such as PICOS, funding sources) and any assumptions and simplifications made	Methods
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis	Methods
Summary measures	13	State the principal summary measures (such as risk ratio, difference in means).	Methods
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (such as I^2 statistic) for each meta-analysis	Methods
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (such as publication bias, selective reporting within studies)	Methods
Additional analyses	16	Describe methods of additional analyses (such as sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified	Methods
Results			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram	Results, Supplementary material 4
Study characteristics	18	For each study, present characteristics for which data were extracted (such as study size, PICOS, follow-up period) and provide the citations	Results, Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome-level assessment (see item 12).	Results
Results of individual studies	20	For all outcomes considered (benefits or harms), present for each study (a) simple summary data for each intervention group and (b) effect estimates and confidence intervals, ideally with a forest plot	
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency	Results, Figure 1; Supplementary material 6
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see item 15)	Not applicable
Additional analysis	23	Give results of additional analyses, if done (such as sensitivity or subgroup analyses, meta-regression) (see item 16)	Not applicable
Discussion			
Summary of evidence	24	Summarise the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (such as health care providers, users, and policy makers)	Discussion
Limitations	25	Discuss limitations at study and outcome level (such as risk of bias), and at review level (such as incomplete retrieval of identified research, reporting bias)	Discussion
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research	Discussion
Funding			
Funding	27	Describe sources of funding for the systematic review and other support (such as supply of data) and role of funders for the systematic review	Pages 4-5

Supplementary Material 2. MOOSE checklist

Markers of liver injury and clinical outcomes in COVID-19 patients: A systematic review and meta-analysis

Criteria		Brief description of how the criteria were handled in the review
Reporting of background		
√	Problem definition	It is uncertain if circulating levels of markers of liver injury at admission could predict clinical outcomes in COVID-19 patients
√	Hypothesis statement	In patients with COVID-19, do levels of admission liver injury biomarkers influence clinical outcomes?
√	Description of study outcomes	Mortality, Severe disease, Respiratory failure, Acute respiratory distress syndrome, Poor clinical outcome
√	Type of exposure	Liver injury markers at admission
√	Type of study designs used	Observational cohort designs and clinical studies
√	Study population	Adult patients with COVID-19
Reporting of search strategy should include		
√	Qualifications of searchers	Setor K. Kunutsor, PhD
√	Search strategy, including time period included in the synthesis and keywords	Time period: from inception to 5 May 2020 The detailed search strategy can be found in Supplementary Material 3
√	Databases and registries searched	MEDLINE, Embase and The Cochrane Library
√	Search software used, name and version, including special features	OvidSP was used to search Embase and MEDLINE EndNote X9 used to manage references
√	Use of hand searching	We searched bibliographies of retrieved papers
√	List of citations located and those excluded, including justifications	Details of the literature search process are outlined in the flow chart. The citation list for excluded studies are available on request.
√	Method of addressing articles published in languages other than English	Not applicable
√	Method of handling abstracts and unpublished studies	Not applicable
√	Description of any contact with authors	None
Reporting of methods should include		
√	Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	Detailed inclusion and exclusion criteria are described in the Methods section.
√	Rationale for the selection and coding of data	Data extracted from each of the studies were relevant to the population characteristics, study design, exposure, and outcome.
√	Assessment of confounding	We assessed confounding by ranking individual studies on the basis of different adjustment levels and performed sub-group analyses to evaluate differences in the overall estimates according to levels of adjustment.
√	Assessment of study quality, including blinding of quality assessors; stratification or regression on possible predictors of study results	Study quality was assessed based on the nine-star Newcastle–Ottawa Scale using pre-defined criteria namely: population representativeness, comparability (adjustment of confounders), ascertainment of outcome. Sensitivity analyses by several quality indicators such as study size, duration of follow-up, and adjustment factors.
√	Assessment of heterogeneity	Results
√	Description of statistical methods in sufficient detail to be replicated	Described in methods section
√	Provision of appropriate tables and graphics	Table 1; Figure 1; Supplementary material 6
Reporting of results should include		
√	Graph summarizing individual study estimates and overall estimate	Figure 1; Supplementary material 6
√	Table giving descriptive information for each study included	Table 1
√	Results of sensitivity testing	Not applicable
√	Indication of statistical uncertainty of findings	95% confidence intervals were presented with all summary estimates
Reporting of discussion should include		
√	Quantitative assessment of bias	The systematic review is limited in scope, as it involves studies with limited information.

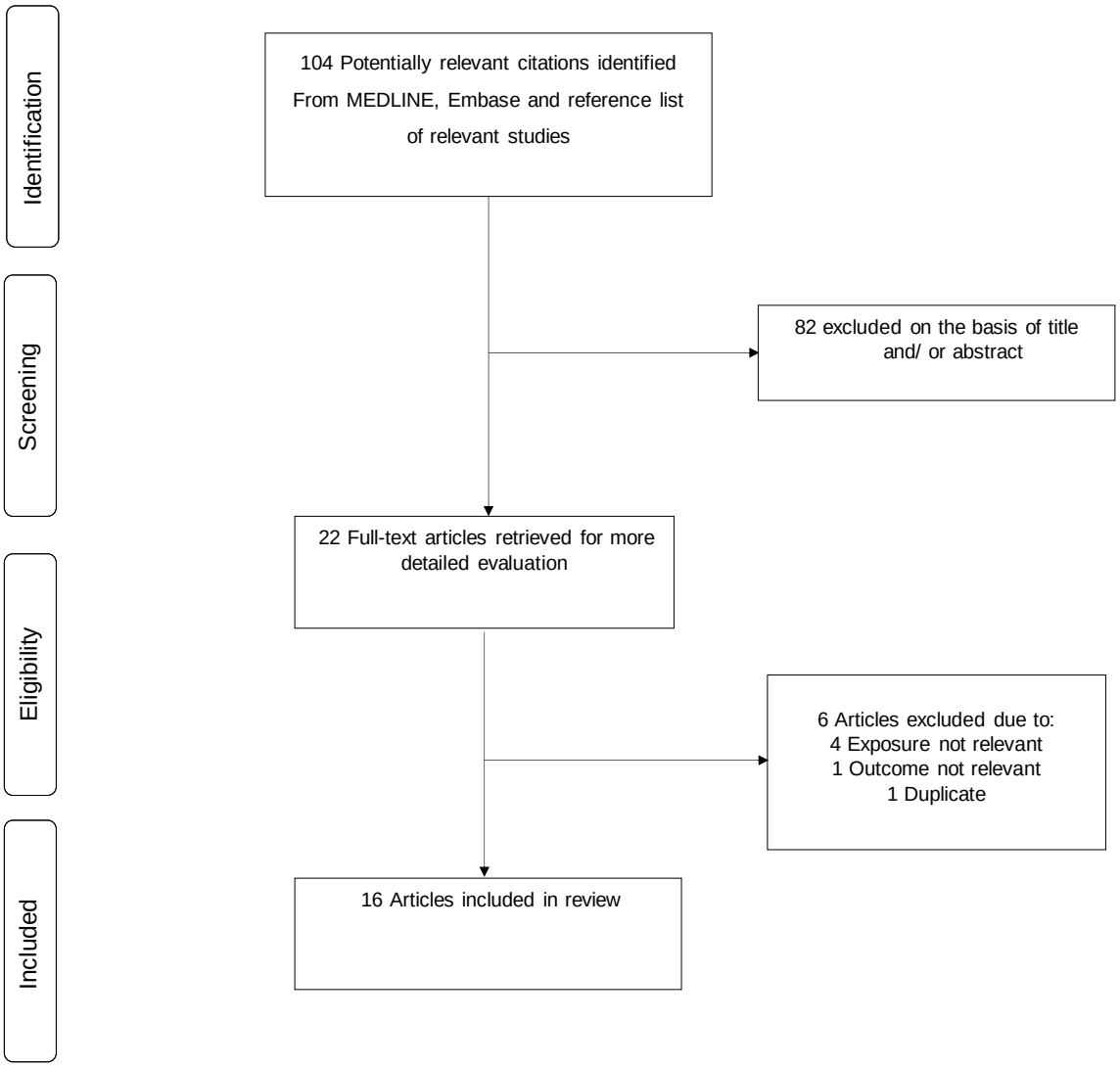
√	Justification for exclusion	All studies were excluded based on the pre-defined inclusion criteria in methods section.
√	Assessment of quality of included studies	Brief discussion included in ‘Methods’ section
Reporting of conclusions should include		
√	Consideration of alternative explanations for observed results	Discussion
√	Generalization of the conclusions	Discussed in the context of the results.
√	Guidelines for future research	We recommend large-scale studies when more data becomes available
√	Disclosure of funding source	In “Acknowledgement” section

Supplementary Material 3: MEDLINE literature search strategy

1 exp gamma-Glutamyltransferase/ (11367)
2 exp Alanine Transaminase/ (31182)
3 exp Aspartate Aminotransferases/ (29579)
4 exp Alkaline Phosphatase/ (54476)
5 exp Bilirubin/ (24525)
6 exp Liver/ (439637)
7 exp Risk Factors/ (814890)
8 1 or 2 or 3 or 4 or 5 or 6 or 7 (1342912)
9 limit 8 to (english language and humans and yr="2019 -Current" and covid-19) (100)

Each part was specifically translated for searching alternative databases.

Supplementary Material 4: Selection of studies included in the meta-analysis



Supplementary Material 5: Reference list of included studies

1. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020 Mar 28;395(10229):1054-62. PubMed PMID: 32171076. Epub 2020/03/15.
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6. Qian GQ, Yang NB, Ding F, Ma AHY, Wang ZY, Shen YF, et al. Epidemiologic and Clinical Characteristics of 91 Hospitalized Patients with COVID-19 in Zhejiang, China: A retrospective, multi-centre case series. QJM. 2020 Mar 17. PubMed PMID: 32181807. Pubmed Central PMCID: PMC7184349. Epub 2020/03/18.
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14. Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med. 2020 Feb 24. PubMed PMID: 32105632. Pubmed Central PMCID: PMC7102538. Epub 2020/02/28.
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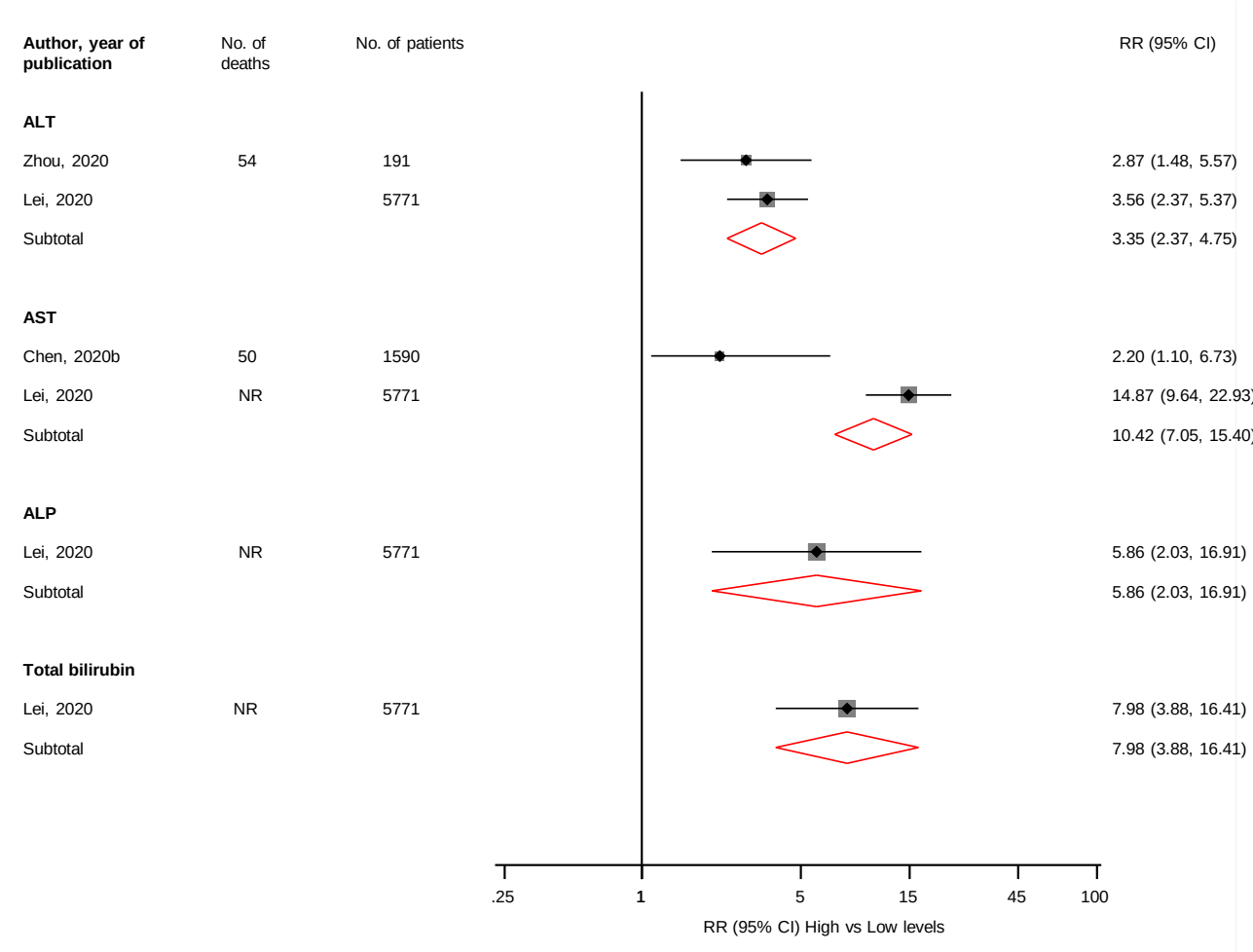
16. Wang L, He W, Yu X, Hu D, Bao M, Liu H, et al. Coronavirus disease 2019 in elderly patients: Characteristics and prognostic factors based on 4-week follow-up. J Infect. 2020 Mar 30. PubMed PMID: 32240670. Pubmed Central PMCID: PMC7118526. Epub 2020/04/03.

Supplementary Material 6: Associations of markers of liver injury with risk of mortality in COVID-19 patients



ALT, alanine aminotransferase; ALP, alkaline phosphatase; AST, aspartate aminotransferase; CI, confidence interval (bars); NR, not reported; RR, relative risk

Table 1. Baseline characteristics of included studies of COVID-19 patients

Author, year of publication	Source of participants	Country	Date of data collection	Mean/median Age (yrs)	Male %	Total participants	No. of outcomes	Outcomes	NOS score
Zhou, 2020	Jinyintan Hospital and Wuhan Pulmonary Hospital	China	Dec 2019 - Jan 2020	56.0	62.0	191	54	In-hospital mortality	5
Huang, 2020	Jin Yintan Hospital	China	Dec 2019 - Jan 2020	49.0	73.0	41	13	ICU care	4
Ruan, 2020	Jin Yin-tan Hospital and Tongji Hospital	China	NR	57.7	68.0	150	68	Mortality	4
Guan, 2020	National Health Commission	China	Dec 2019 - Jan 2020	47.0	58.1	1099	173 (67)	Severe disease (Composite outcome of ICU admission, the use of mechanical ventilation, or death)	4
Liu, 2020	3 tertiary hospitals in Wuhan	China	Dec 2019 - Jan 2020	38.0	50.0	78	11	Severe disease	5
Qian, 2020	5 hospitals in Zhejiang province	China	Jan - Feb 2020	50.0	40.7	91	9	Severe disease	4
Zheng, 2020	North Hospital of Changsha first Hospital	China	Jan - Feb 2020	45.0	49.7	161	30	Severe disease	4
Wang, 2020	Zhongnan Hospital of Wuhan University	China	Jan, 2020	56.0	54.3	138	36	ICU care	4
Wang, 2020b	Union Hospital in Wuhan	China	Jan - Feb 2020	42.0	46.0	69	14	SpO_2<90%	4
Wang, 2020c	Renmin Hospital of Wuhan University	China	Jan – Feb 2020	71.0	49.0	339	65	Mortality	4
Chen, 2020	Tongji Hospital in Wuhan	China	Jan - Feb 2020	62.0	62.0	274	113	Mortality	4
Chen, 2020b	National Health Commission	China	Dec 2019 - Jan 2020	NR	NR	1,590	50	Mortality	6
Cai, 2020	Third People's Hospital of Shenzhen	China	Jan - Feb 2020	47.0	47.5	417	91	Severe disease	6
Yang, 2020	Wuhan Jin Yin-tan hospital	China	Dec 2019 – Jan 2020	59.7	67.0	52	32	Mortality	4
Lei, 2020	10 hospitals in Hubei Province	China	Dec 2019 – Mar 2020	56.0	47.2	5,771	1,186	Severe disease	5
Xie, 2020	Jinyintan Hospital	China	Feb 2020	60.0	55.7	79	28	Severe disease	4

ICU, intensive care unit; NOS, Newcastle-Ottawa Scale; NR, not reported